10/771,774

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2619	((544/284) or (544/293) or (544/244) or (544/122)).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2006/09/11 11:53
L2	239	(423/316).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2006/09/11 11:53
L3	1074	((514/87) or (514/234.5) or (514/266.2)).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2006/09/11 11:53
L4	2381	L1	US-PGPUB; USPAT	OR	OFF	2006/09/11 11:53
L5	3203	L1 or L2 or L3 or L4	US-PGPUB; USPAT	OR	OFF	2006/09/11 11:54
L6	547	L5 and (anilino or phenylamino)	US-PGPUB; USPAT	OR	OFF	2006/09/11 11:54
L7	338	L6 and (quinazolin or quinazolinyl or quinazoline)	US-PGPUB; USPAT	OR	OFF	2006/09/11 11:54

10/ 771,774

Connecting via Winsock to STN

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LOGINID:ssspta1202txn

PASSWORD:
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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS 4	MAY 10	CA/CAplus enhanced with 1900-1906 U.S. patent records
NEWS 5	MAY 11	KOREAPAT updates resume
NEWS 6	MAY 19	Derwent World Patents Index to be reloaded and enhanced
NEWS 7	MAY 30	IPC 8 Rolled-up Core codes added to CA/CAplus and USPATFULL/USPAT2
NEWS 8	MAY 30	The F-Term thesaurus is now available in CA/CAplus
NEWS 9	JUN 02	The first reclassification of IPC codes now complete in INPADOC
NEWS 10	JUN 26	TULSA/TULSA2 reloaded and enhanced with new search and and display fields
NEWS 11	JUN 28	Price changes in full-text patent databases EPFULL and PCTFULL
NEWS 12	JUl 11	CHEMSAFE reloaded and enhanced
NEWS 13	JUl 14	FSTA enhanced with Japanese patents
NEWS 14	JUl 19	Coverage of Research Disclosure reinstated in DWPI
NEWS 15	AUG 09	INSPEC enhanced with 1898-1968 archive
NEWS 16	AUG 28	ADISCTI Reloaded and Enhanced
NEWS 17	AUG 30	CA(SM)/CAplus(SM) Austrian patent law changes

NEWS EXPRESS JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8
NEWS X25	X.25 communication option no longer available

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 09:54:02 ON 11 SEP 2006

=> file reg
COST IN U.S. DOLLARS SINCE FILE TOTAL

10/ 771,774

	ENTRY	SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 09:54:17 ON 11 SEP 2006

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 10 SEP 2006 HIGHEST RN 906318-57-8
DICTIONARY FILE UPDATES: 10 SEP 2006 HIGHEST RN 906318-57-8

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

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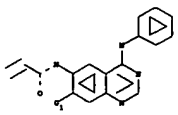
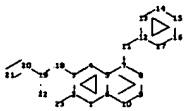
REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10771774.str





chain nodes :
11 18 19 20 21 22 23
ring nodes :
1 2 3 4 5 6 7 8 9 10 12 13 14 15 16 17
chain bonds :
2-23 3-18 7-11 11-12 18-19 19-20 19-22 20-21
ring bonds :

10/ 771,774

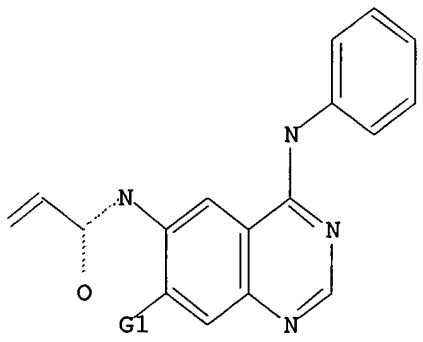
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 12-13 12-17 13-14 14-15
15-16 16-17
exact/norm bonds :
2-23 3-18 7-11 11-12 18-19 19-22
exact bonds :
19-20 20-21
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 12-13 12-17 13-14 14-15
15-16 16-17
isolated ring systems :
containing 1 : 12 :

G1:O,S,N

Hydrogen count :
9:= exact 1
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:CLASS 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:CLASS
20:CLASS 21:CLASS 22:CLASS 23:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



G1 O,S,N

Structure attributes must be viewed using STN Express query preparation.

=> s l1 ful
FULL SEARCH INITIATED 09:54:39 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 561 TO ITERATE

100.0% PROCESSED 561 ITERATIONS 416 ANSWERS
SEARCH TIME: 00.00.01

L2 416 SEA SSS FUL L1

=> file hcaplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION

10/ 771,774

FULL ESTIMATED COST 166.94 167.15

FILE 'HCAPLUS' ENTERED AT 09:54:47 ON 11 SEP 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 11 Sep 2006 VOL 145 ISS 12
FILE LAST UPDATED: 10 Sep 2006 (20060910/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s l2
L3          130 L2

=> s l3 not py>2003
       3249455 PY>2003
L4           25 L3 NOT PY>2003

=> d his

     (FILE 'HOME' ENTERED AT 09:54:02 ON 11 SEP 2006)

     FILE 'REGISTRY' ENTERED AT 09:54:17 ON 11 SEP 2006
L1               STRUCTURE UPLOADED
L2           416 S L1 FUL

     FILE 'HCAPLUS' ENTERED AT 09:54:47 ON 11 SEP 2006
L3           130 S L2
L4            25 S L3 NOT PY>2003

=> d l4 1- ibib abs hitstr
YOU HAVE REQUESTED DATA FROM 25 ANSWERS - CONTINUE? Y/(N):y
```

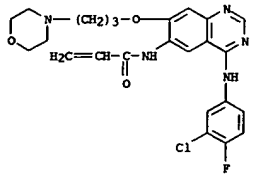
L4 ANSWER 1 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:197494 HCAPLUS
DOCUMENT NUMBER: 141:235330
TITLE: Emerging roles of targeted small molecule protein-tyrosine kinase inhibitors in cancer therapy
AUTHOR(S): Smith, John K.; Mamoon, Naila M.; Duhe, Roy J.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Mississippi Medical Center, Jackson, MS, 39216-4505, USA
SOURCE: Oncology Research (2003), 14(4/5), 175-225
CODEN: ONREE8; ISSN: 0965-0407
PUBLISHER: Cognizant Communication Corp.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Targeted protein-tyrosine kinase inhibitors (PTKIs) comprise a new, rapidly evolving class of low mol. weight anticancer drugs. Two members of this class, imatinib (Gleevec) and gefitinib (Iressa), are currently approved for market use in the United States. This review discusses the scientific history behind these two PTKI drugs, including the role of the targeted kinase in cancer etiol., the biochem. of selective inhibition, the evaluation of clin. efficacy, and the mechanisms whereby drug resistance has emerged. Other PTKIs undergoing clin. evaluation are also described, including epidermal growth factor receptor kinase inhibitors (erlotinib, PKI166, and CI-1033) and PTKIs designed to disrupt tumor vascularization (SU5416, SU6668, SU11248, PTK787, and ZD6474). How might one apply current knowledge to the efficient development of new agents that would target as-yet-unexploited oncogenic PTKs such as chimeric anaplastic leukemia kinases or Janus kinases. Ideally, the targets should contain structurally distinct drug interaction epitopes, although it is not necessary that these epitopes be unique to a single target, because effective drugs may inhibit multiple kinases involved in an oncogenic process. Oral availability is a highly desirable feature because daily oral administration can maintain a sustained efficacious plasma concentration, whereas intermittent parenteral administration may not. Perhaps most importantly, one must verify the presence of an appropriate mol. target on a case-by-case basis before selecting a patient for PTKI therapy. Thus, the development of molecularly targeted diagnostic tools will be crucial to the ultimate success of molecularly targeted PTKI therapy.

IT 289499-45-2, CI-1033
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epidermal growth factor receptor kinase inhibitor CI-1033 is designed to disrupt tumor vascularization and used in treatment of cancer therapy)

RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 1 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



●2 HCl

REFERENCE COUNT: 422 THERE ARE 422 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

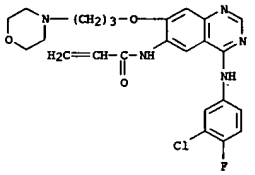
L4 ANSWER 2 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:1000449 HCAPLUS
DOCUMENT NUMBER: 140:35213
TITLE: CI-1033, an irreversible pan-erbB receptor inhibitor and its potential application for the treatment of breast cancer
AUTHOR(S): Allen, Lee F.; Eiseman, Irene A.; Fry, David W.; Lenehan, Peter F.
CORPORATE SOURCE: Departments of Clinical Development, Oncology and Cancer Pharmacology, Pfizer Global Research and Development, Ann Arbor Laboratories, Ann Arbor, MI, USA
SOURCE: Seminars in Oncology (2003), 30(5, Suppl. 16), 65-78
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The erbB family of cell surface receptor proteins consists of four members, all of which play a role in the development and growth of the normal breast. The activity of this signaling pathway is normally tightly controlled, and dysregulation has been shown to play a significant role in the pathogenesis and progression of breast and other cancers. The potent transforming potential of these receptors is further enhanced by the coexpression of multiple members of this receptor family, which worsens prognosis. Therapeutic blockade of erbB-2 receptor signaling has to date been shown to be effective in only a subset of chemotherapy-resistant breast cancer patients. CI-1033 is a highly potent and selective pan-erbB inhibitor that efficiently blocks signal transduction through all four members of the erbB receptor family. In addition, it covalently binds to these receptors, irreversibility inhibiting them, and thereby provides for prolonged suppression of erbB receptor-mediated signaling. Clin., it has been shown to have an acceptable side effect profile at potentially therapeutic doses and schedules. Biomarker studies have shown target inhibition in patients, and evidence of antitumor activity has also been observed in phase I studies. Given the broad expression pattern of the erbB family of receptors in solid tumors, and the important proliferative effect of co-expression of multiple erbB receptors, CI-1033, as an irreversible, pan-erbB inhibitor, has the potential to have an important role in the future treatment of breast and other cancers.

IT 289499-45-2, CI-1033
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(potential use of pan-erbB receptor inhibitor CI-1033 for treatment of breast cancer)

RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 2 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



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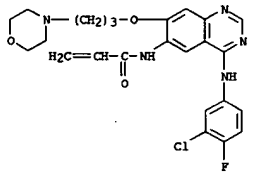
REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:8967 HCAPLUS
DOCUMENT NUMBER: 139:62338
TITLE: Small molecule tyrosine kinase inhibitors: clinical development of anticancer agents
AUTHOR(S): Laird, A. Douglas; Cherrington, Julie M.
CORPORATE SOURCE: SUGEN, Inc., South San Francisco, CA, 94080, USA
SOURCE: Expert Opinion on Investigational Drugs (2003), 12(1), 51-64
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Numerous small mol. synthetic tyrosine kinase inhibitors are in clin. development for the treatment of human cancers. These fall into three broad categories: inhibitors of the epidermal growth factor receptor tyrosine kinase family (e.g., Iressa and Tarceva), inhibitors of the split kinase domain receptor tyrosine kinase subgroup (e.g., PTK787/ZK 222584 and SU11248) and inhibitors of tyrosine kinases from multiple subgroups (e.g., Gleevec). In addition, agents targeting other tyrosine kinases implicated in cancer, such as Met, Tie-2 and Src, are in preclin. development. As experience is gained in the clinic, it has become clear that unleashing the full therapeutic potential of tyrosine kinase inhibitors will require patient preselection, better assays to guide dose selection, knowledge of mechanism-based side effects and ways to predict and overcome drug resistance.
IT 289499-45-2, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small mol. tyrosine kinase inhibitors and clin. development of anticancer agents)
RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



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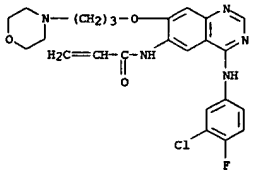
REFERENCE COUNT: 127 THERE ARE 127 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

L4 ANSWER 3 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)
FORMAT

L4 ANSWER 4 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:974164 HCAPLUS
DOCUMENT NUMBER: 139:143003
TITLE: Clinical evaluation of agents targeting epidermal growth factor receptor (EGFR) in cancer
AUTHOR(S): Lin, Edward H.; Abbruzzese, James L.
CORPORATE SOURCE: Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
SOURCE: Oncogene-Directed Therapies (2003), 313-330.
Editor(s): Rak, Janusz. Humana Press Inc.: Totowa, N. J.
CODEN: 69DKTX; ISBN: 0-89603-982-X
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review. Proteins encoded by oncogenes and tumor-suppressor genes are the essential signaling components of the complex cellular signaling networks. Cancer arises from a multi-step process promoted by the imbalanced growth signals as a consequence of gain of oncogene and/or loss of tumor suppressor genes. The six essential cancer hallmarks include persistent cell growth signals, insensitivity to anti-growth signals, evasion of apoptosis, persistent angiogenesis, gain of cell immortality, and tumor invasion and metastasis. As an oncogene, gain of epidermal growth factor receptor (EGFR) function is achieved through EGFR over-expression and has been shown to be associated with almost all the six essential hallmarks of cancer except the gain of cell immortality. In various exptl. models, EGFR inhibition leads to regression of tumor cell growth, inhibition of angiogenesis, induction of apoptosis, and inhibition of tumor invasion and metastasis. Furthermore, over-expression of EGFR, frequently observed in a number of human cancers, is associated with poor overall prognosis, increased tumor recurrence, and decreased patient survival. The hypothesis that EGFR might be a cancer therapeutic target was proposed by Mendelsohn in the early 1980s; emerging only recently are the promising clin. trial results from a number of EGFR antagonists in different human cancers. This review will discuss the clin. developments and future directions of EGFR antagonists in cancer treatment.
IT 289499-45-2, CI-1033
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. evaluation of agents targeting epidermal growth factor receptor (EGFR) in cancer)
RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 4 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

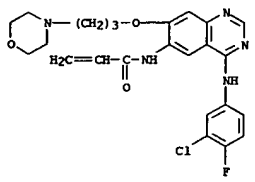


●2 HCl

REFERENCE COUNT: 135 THERE ARE 135 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:651435 HCAPLUS
DOCUMENT NUMBER: 138:180074
TITLE: Potential benefits of the irreversible pan-erbB inhibitor, CI-1033, in the treatment of breast cancer
AUTHOR(S): Allen, Lee F.; Lenehan, Peter F.; Eiseman, Irene A.; Elliott, William L.; Fry, David W.
CORPORATE SOURCE: Departments of Clinical Development, Oncology, and Cancer Pharmacology, Pfizer Global Research and Development, Ann Arbor, MI, USA
SOURCE: Seminars in Oncology (2002), 29(3, Suppl. 11), 11-21
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Transmembrane receptor Tyr kinases were shown to play an important role in the modulation of growth factor signaling and regulation of key cellular processes. The erbB receptor family is part of the receptor Tyr kinase superfamily and consists of 4 members, erbB-1, erbB-2, erbB-3, and erbB-4. A majority of solid tumors express 1 or more members of this receptor family, and coexpression of multiple erbB receptors leads to an enhanced transforming potential and worsened prognosis. The erbB receptor family was shown to play an important role in both the development of the normal breast and in the pathogenesis and progression of breast cancer. Receptor overexpression was also shown to be a neg. prognostic indicator and to correlate with both tumor invasiveness and a lack of responsiveness to standard treatment. Clin., blockade of the erbB-2 receptor has recently been shown to provide benefit in a subset of chemotherapy-resistant breast cancer patients. CI-1033 is an orally available pan-erbB receptor Tyr kinase inhibitor that, unlike the majority of receptor inhibitors, effectively blocks signal transduction through all 4 members of the erbB family. In addition, it blocks the highly tumorigenic, constitutively activated variant of erbB-I, EGFRvIII, and inhibits downstream signaling through both the Ras/MAP kinase, and PI-3 kinase/AKT pathways. CI-1033 is also unique in that it is an irreversible inhibitor, thereby providing prolonged suppression of erbB receptor-mediated signaling. Preclin. data have shown CI-1033 to be efficacious against a variety of human tumors in mouse xenograft models, including breast carcinomas. In a phase I study, CI-1033 was shown to have an acceptable side effect profile at potentially therapeutic dose levels and demonstrates evidence of target biomarker modulation. Antitumor activity was also observed in this study, including 1 partial clin. response and stable disease in over 30% of patients, including 1 patient with heavily pretreated breast cancer. By virtue of its pan-erbB receptor inhibition and potent interruption of downstream mitogenic signaling pathways, CI-1033 may have clin. activity for solid tumors that overexpress 1 erbB family member, coexpress multiple members of the erbB family, or express a constitutively activated, mutated form of these receptors. Given the important role of the erbB receptor family in the pathogenesis and progression of breast cancer, an irreversible pan-erbB inhibitor like CI-1033 could have an important role to play in the future treatment of breast cancer.
IT 289499-45-2, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CI-1033 in treatment of breast cancer)

L4 ANSWER 5 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)
RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



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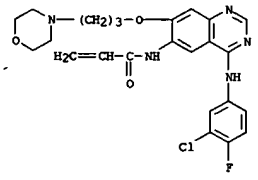
REFERENCE COUNT: 108 THERE ARE 108 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:604225 HCAPLUS
DOCUMENT NUMBER: 138:162767
TITLE: EGF signal transduction and its molecular targeted drugs against cancer
AUTHOR(S): Sone, Saburo; Yamamoto, Akihiko
CORPORATE SOURCE: Dep. Internal Med. Molecular Therapeutics, Univ. Tokushima Sch. Med., Japan
SOURCE: Saishin Igaku (2002), 57(7), 1712-1717
CODEN: SAIGAK; ISSN: 0370-8241
PUBLISHER: Saishin Igakusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review. The epidermal growth factor receptor (EGFR) and its inhibition in cancer therapy is reviewed together with the mechanism related to EGF signal transduction of antitumor agents such as EGFR antibody (C225) and EGFR tyrosine kinase inhibitors (ZD1839, OSI-774, and CI-1033).
IT 289499-45-2, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(EGF signal transduction and its mol. targeted drugs against cancer)
RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



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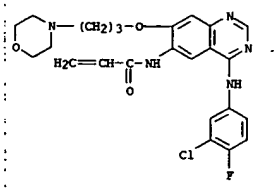
L4 ANSWER 7 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:414301 HCAPLUS
DOCUMENT NUMBER: 138:32893
TITLE: Drug-induced ubiquitylation and degradation of ErbB receptor tyrosine kinases: implications for cancer therapy
AUTHOR(S): Citri, Ami; Alroy, Iris; Lavi, Sara; Rubin, Chanan; Xu, Wanping; Grammatikakis, Nicolas; Patterson, Cam; Neckers, Len; Fry, David W.; Yarden, Yosef
CORPORATE SOURCE: Department of Biological Regulation, The Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: EMBO Journal (2002), 21(10), 2407-2417
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Overexpression of ErbB-2/HER2 is associated with aggressive human malignancies, and therapeutic strategies targeting the oncoprotein are currently in different stages of clin. application. Tyrosine kinase inhibitors (TKIs) that block the nucleotide-binding site of the kinase are especially effective against tumors. Here the authors report an unexpected activity of TKIs: along with inhibition of tyrosine phosphorylation, they enhance ubiquitylation and accelerate endocytosis and subsequent intracellular destruction of ErbB-2 mols. Especially potent is an irreversible TKI (CI-1033) that alkylates a cysteine specific to ErbB receptors. The degradative pathway stimulated by TKIs appears to be chaperone mediated, and is common to the heat shock protein 90 (Hsp90) antagonist geldanamycin and a stress-induced mechanism. In agreement with this conclusion, CI-1033 and geldanamycin additively inhibit tumor cell growth. Based upon a model for drug-induced degradation of ErbB-2, the authors propose a general strategy for selective destruction of oncoproteins by targeting their interaction with mol. chaperones.
IT 289499-45-2, CI-1033
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug-induced ubiquitylation and degradation of ErbB receptor tyrosine kinases and implications for cancer therapy with tyrosine kinase inhibitors and Hsp90 antagonist geldanamycin)
RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 7 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



●2 HCl

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

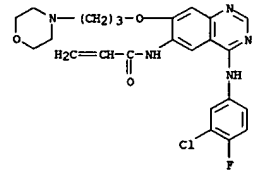
ACCESSION NUMBER: 2002:122440 HCAPLUS
DOCUMENT NUMBER: 137:329330
TITLE: Evaluation of the human serum albumin column as a discovery screening tool for plasma protein binding
AUTHOR(S): Buchholz, Lisa; Cai, Chun-Hua; Andress, Larry; Cleton, Adriaan; Brodfuehrer, Joanne; Cohen, Lucinda
CORPORATE SOURCE: Dynamics and Metabolism, Department of Pharmacokinetics, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
SOURCE: European Journal of Pharmaceutical Sciences (2002), 15(2), 209-215
CODEN: EPSCED; ISSN: 0928-0987
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A total of 69 compds. with a variety of chemical structures were assayed using a human serum albumin column in combination with UV and mass spectrometric detection. A moderate correlation, R2=0.661, between the plasma protein binding, determined by traditional techniques of equilibrium dialysis or ultrafiltration, and chromatog. retention factor (k'/k'+1) was observed Disparity between the regression line and numerous samples was observed across the entire range of plasma protein binding. Attempts to discriminate between compds. from the data set to achieve better correlation based physico-chemical properties were unsuccessful. Good agreement was observed for retention times obtained with UV detection with mobile phase containing phosphate buffer and mass spectrometric detection with mobile phase containing acetate buffer. Essentially identical data were obtained for compds. analyzed in singlet or cassette for minimally or highly bound (>90% bound) compds. Anal. of cassettes containing compds. with plasma protein binding greater than 90% did not cause column overload, even at analyte concns. up to 100 μg/mL. Diverse results were obtained when chromatog. retention was used to rank order various classes of compds. Better correlation with ordering from known binding was obtained when a compound class contained a wide range of protein binding, in contrast to when compds. within a given class were all highly bound.

IT 289499-45-2, PD 0183805
RL: ANT (Analyte); ANST (Analytical study)
(evaluation of human serum albumin column as a discovery screening tool for plasma protein binding)

RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 8 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



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REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

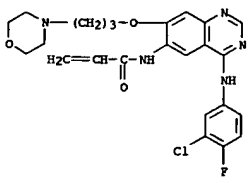
ACCESSION NUMBER: 2002:86818 HCAPLUS
DOCUMENT NUMBER: 136:395481
TITLE: Differential sensitivity of cancer cells to inhibitors of the epidermal growth factor receptor family
AUTHOR(S): Bishop, Philippe C.; Myers, Timothy; Robey, Robert; Fry, David W.; Liu, Edison T.; Blagosklonny, Mikhail V.; Bates, Susan E.
CORPORATE SOURCE: Medicine Branch, NCI, NIH, Bethesda, MD, 20892, USA
SOURCE: Oncogene (2002), 21(1), 119-127
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Clin. responses to the HER1 (EGF receptor) inhibitors and HER2/neu/ErbB2 inhibitors correlate with high levels of receptor expression. However, a significant subset of patients with high receptor levels appear to be refractory to treatment. We have observed similar results in the 60 cell lines of the NCI Anti-Cancer Drug Screen using a panel of 11 selective HER1 inhibitors. As expected, low HER1-expressing cell lines were insensitive to HER1 inhibitors. In cell lines with high HER1 expression, low concns. of HER1 inhibitors potently inhibit both HER1 phosphorylation and the mitogen-activated protein kinase (MAPK) pathway. However, this inhibition did not always correlate with cellular arrest. High HER1-expressing cell lines can be subdivided into two groups based on their sensitivity to HER1 inhibitors. In the sensitive group, receptor and growth inhibition was concordant and occurred at submicromolar concns. of HER1 inhibitors. In the insensitive group, receptor inhibition occurred at a low concentration (< 1 M) but concns. that were ten times or higher were required for growth inhibition. Also, neither induction of p21 and cyclin D1 nor p53 status could explain the difference between sensitive and insensitive cells. Although EGF activated the MAPK pathway in all cell lines, only drug-sensitive cell lines responded to EGF (accelerated entry from G1 to S) and to HER1 inhibitors (G1 arrest) by changes in cell cycling. Furthermore, an EGF-dependent immortalized mammary epithelial cell line was extremely sensitive to a panel of HER1 inhibitors. We infer that independence from mitogen-mediated signaling confers insensitivity to HER1 inhibitors in a large subset of cancer cell lines.

IT 289499-45-2, NSC 709239
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PD 183805; sensitivity of cancer cells to inhibitors of EGF receptor family)

RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 9 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



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REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

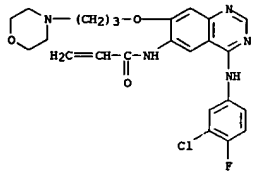
L4 ANSWER 10 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:74864 HCAPLUS
DOCUMENT NUMBER: 137:134227
TITLE: Epidermal growth factor receptor tyrosine kinase inhibitors in cancer therapy
AUTHOR(S): Adjei, Alex A.
CORPORATE SOURCE: Division of Medical Oncology, Mayo Clinic and Foundation, Rochester, MN, 55905, USA
SOURCE: Drugs of the Future (2001), 26(11), 1087-1092
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Receptor tyrosine kinases are transmembrane proteins involved in signal transduction. They propagate growth factor signals from the cell surface to intracellular processes that control critical functions such as growth, differentiation, angiogenesis and inhibition of apoptosis. In malignancies, these signaling pathways are often exploited to optimize tumor growth and metastasis. One such family of receptor tyrosine kinases is the epidermal growth factor receptor (EGFR) tyrosine kinase. These receptors are overexpressed in a wide variety of epithelial cancers and have been implicated in tumor aggressiveness. Thus, targeting the EGFR tyrosine kinase has attracted considerable attention. This review will summarize current preclin. and clin. knowledge of the small-mol. oral inhibitors of the EGFR tyrosine kinase, which include ZD-1839, OSI-774, CI-1033, EKB-569, PKI-166, GW-2016 and BIBX-1382.

IT 289499-45-2, CI-1033
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epidermal growth factor receptor tyrosine kinase inhibitors in cancer therapy)

RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



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REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

L4 ANSWER 11 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:935435 HCAPLUS
DOCUMENT NUMBER: 136:84677
TITLE: Methods for enhancing antibody-induced cell lysis and treating cancer
INVENTOR(S): Weiner, George; Hartmann, Gunther
PATENT ASSIGNEE(S): University of Iowa Research Foundation, USA
SOURCE: PCT Int. Appl., 312 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

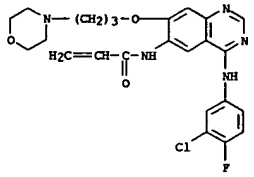
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001097843	A2	20011227	WO 2001-US20154	20010622
WO 2001097843	A3	20030123		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2410371	AA	20011227	CA 2001-2410371	20010622
US 2003026801	A1	20030206	US 2001-888326	20010622
EP 1296714	A2	20030402	EP 2001-948684	20010622
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003535907	T2	20031202	JP 2002-503327	20010622
PRIORITY APPLN. INFO.:			US 2000-213346P P	20000622
			WO 2001-US20154 W	20010622

AB The invention relates to methods and products for treating cancer. In particular the invention relates to combinations of nucleic acids and antibodies for the treatment and prevention of cancer. The invention also relates to diagnostic methods for screening cancer cells.

IT 289499-45-2, PD 183805
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunostimulatory nucleic acids and antibody specific to CD20, CD22, CD19 or CD40 for inducing cell lysis and treating cancer)

RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 11 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



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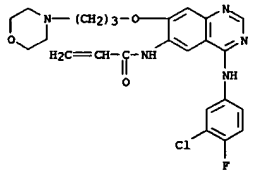
L4 ANSWER 12 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



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REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:921399 HCAPLUS
DOCUMENT NUMBER: 137:72358
TITLE: CI-1033, a pan-erbB tyrosine kinase inhibitor
AUTHOR(S): Slichenmyer, William J.; Elliott, William L.; Fry, David W.
CORPORATE SOURCE: Department of Cancer Research, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
SOURCE: Seminars in Oncology (2001), 28(5, Suppl. 16), 80-85
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Overexpression of the erbB family of receptor tyrosine kinases has been implicated in a variety of tumors including breast, lung, prostate, and brain. Most solid tumors express one or more of these receptors, which can often be related to tumor aggressiveness and poor patient prognosis. CI-1033, a pan-erbB tyrosine kinase inhibitor, is a clin. promising agent that is active against all four members of the erbB receptor tyrosine kinase family. In vitro studies of human cancer cell lines indicate that CI-1033 results in prompt, potent, and sustained inhibition of tyrosine kinase activity. This inhibition is highly selective for erbBI (epidermal growth factor receptor), erbB2, erbB3, and erbB4 without inhibiting tyrosine kinase activity of receptors such as platelet-derived growth factor receptor, fibroblast growth factor receptor, and insulin receptor, even at high concns. Treatment of athymic nude mice bearing xenografts of human A431 epidermoid carcinoma, H125 non-small cell lung carcinoma, and SF-767 glioblastoma results in highly significant suppression of tumor growth. The major toxicity in animals is diarrhea, which is more severe at higher doses. In animal models, all side effects are reversible on cessation of treatment. Thus, CI-1033, which is currently undergoing phase I clin. trials, holds significant potential for use in a broad range of solid tumors.

IT 289499-45-2, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CI-1033, a pan-erbB tyrosine kinase inhibitor)

RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

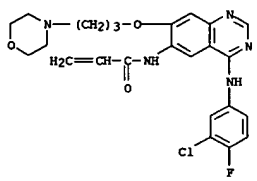
L4 ANSWER 13 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:921398 HCAPLUS
DOCUMENT NUMBER: 137:87979
TITLE: Anticancer therapy targeting the ErbB family of receptor tyrosine kinases
AUTHOR(S): Slichenmyer, William J.; Fry, David W.
CORPORATE SOURCE: Departments of Oncology Clinical Development and Cancer Research, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
SOURCE: Seminars in Oncology (2001), 28(5, Suppl. 16), 67-79
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Several agents that target one or more members of the erbB family of receptor tyrosine kinases are currently undergoing clin. investigation. The monoclonal antibody trastuzumab has been shown effective in erbB2-expressing metastatic breast cancer when administered as a single agent or in combination with cytotoxic chemotherapy. Toxicities associated with trastuzumab include infusion-related fever and chills, hypersensitivity reactions, and congestive heart failure. C225 is a monoclonal antibody directed against the epidermal growth factor receptor, which has shown encouraging antitumor activity in early clin. development. The orally active tyrosine kinase inhibitors show encouraging antitumor activity in preclin. models and early clin. trials. Members of this class currently in clin. development include ZD1839, OSI774, and CI-1033. Evidence to data suggests that the major role for erbB receptor-targeting drugs will be in combined therapy to enhance response to cytotoxic drugs, and in long-term monotherapy to maintain response and prevent disease progression or recurrence.

IT 289499-45-2, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticancer therapy targeting the ErbB family of receptor tyrosine kinases)

RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



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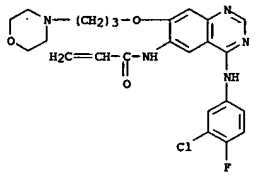
REFERENCE COUNT: 125 THERE ARE 125 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

L4 ANSWER 13 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)
FORMAT

L4 ANSWER 14 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:800795 HCAPLUS
DOCUMENT NUMBER: 136:95729
TITLE: Evidence for epidermal growth factor receptor-enhanced chemosensitivity in combinations of cisplatin and the new irreversible tyrosine kinase inhibitor CI-1033
AUTHOR(S): Gieseg, Michael A.; De Bock, Charles; Ferguson, Lynnette R.; Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of Medical & Health Sciences, The University of Auckland, Auckland, 1000, N. Z.
SOURCE: Anti-Cancer Drugs (2001), 12(8), 683-690
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Irreversible inhibitors of the epidermal growth factor receptor (EGFR) are showing promise in clin. trials. This report is the first to show that inhibition of the EGFR tyrosine kinase by an irreversible binder synergizes with cisplatin, at least in EGFR-overexpressing tissue culture cell lines in vitro. Unlike previous synergies demonstrated between ErbB2 blockade and DNA-damaging drugs, the synergy between the irreversible EGFR inhibitor and cisplatin does not appear to involve the repair of DNA-cisplatin adducts. Given the current clin. data, this combination may be of more than theor. interest.
IT 289499-45-2, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evidence for EGFR-enhanced chemosensitivity in combinations of cisplatin and CI-1033)
RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



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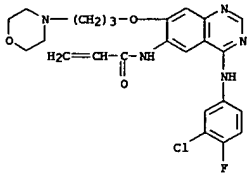
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

L4 ANSWER 15 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:799778 HCAPLUS
DOCUMENT NUMBER: 136:112324
TITLE: Sequential tumor biopsies in early phase clinical trials of anticancer agents for pharmacodynamic evaluation
AUTHOR(S): Dowlati, Afshin; Haaga, John; Remick, Scot C.; Spiro, Timothy P.; Gerson, Stanton L.; Liu, Lili; Berger, Sosamma J.; Berger, Nathan A.; Willson, James K. V.
CORPORATE SOURCE: Division of Hematology/Oncology, Department of Medicine and Developmental Therapeutics Program, Ireland Cancer Center at University Hospitals of Cleveland and Case Western Reserve University, Cleveland, OH, 44106, USA
SOURCE: Clinical Cancer Research (2001), 7(10), 2971-2976
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the setting of target-based anticancer drug development, it is critical to establish that the observed preclin. activity can be attributed to modulation of the intended target in early phase trials in human subjects. This paradigm of target modulation allows the authors to determine a Phase II or III dose (optimal biochem./biol. modulatory dose) that may not necessarily be the maximum tolerated dose. A major obstacle to target-based (often cytostatic) drug development has been obtaining relevant tumor tissue during clin. trials of these novel agents for laboratory anal. of the putative marker of drug effect. From 1989 to present, the authors have completed seven clin. trials in which the end point was a biochem. or biol. modulatory dose in human tumor tissues (not surrogate tissue). Eligibility enrollment required that patients have a biopsiable lesion either with computerized tomog. (CT) guidance or direct visualization and consent to sequential (pre and posttreatment) biopsies. A total of 192 biopsies were performed in 107 patients. All but 8 patients had sequential pre and posttreatment biopsies. Seventy-eight (73%) of the 107 patients had liver lesion biopsies. In eight patients, either one or both biopsies contained insufficient viable tumor tissue or no tumor tissue at all for anal. Of a total of 99 patients in whom the authors attempted to obtain paired biopsies, a total of 87 (88%) were successful. Reasons for failure included patient refusal for a second biopsy (n = 2), vasovagal reaction with first biopsy precluding a second biopsy (n = 1), subcapsular hepatic bleeding (n = 1), and most commonly obtaining necrotic tumor, fibrous, or normal tissue in one of the two sequential biopsies (n = 8). This is the first and largest reported series demonstrating that with adequate precautions and experience, sequential tumor biopsies are feasible and safe during early phase clin. trials.
IT 289499-45-2, CI-1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sequential human tumor biopsies in early phase clin. trials of anticancer agents for pharmacodynamic evaluation)
RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 15 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



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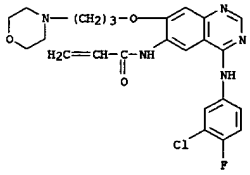
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



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REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:799777 HCAPLUS
DOCUMENT NUMBER: 137:27578
TITLE: A novel approach in the treatment of cancer: Targeting the epidermal growth factor receptor
AUTHOR(S): Ciardiello, Fortunato; Tortora, Giampaolo
CORPORATE SOURCE: Cattedra di Oncologia Medica, Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli "Federico II,", Naples, 80131, Italy
SOURCE: Clinical Cancer Research (2001), 7(10), 2958-2970
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The epidermal growth factor receptor (EGFR) autocrine pathway contributes to a number of processes important to cancer development and progression, including cell proliferation, apoptosis, angiogenesis, and metastatic spread. The critical role the EGFR plays in cancer has led to an extensive search for selective inhibitors of the EGFR signaling pathway. The results of a large body of preclin. studies and the early clin. trials thus far conducted suggest that targeting the EGFR could represent a significant contribution to cancer therapy. A variety of different approaches are currently being used to target the EGFR. The most promising strategies in clin. development include monoclonal antibodies to prevent ligand binding and small mol. inhibitors of the tyrosine kinase enzymic activity to inhibit autophosphorylation and downstream intracellular signaling. At least five blocking monoclonal antibodies have been developed against the EGFR. Among these, IMC-225 is a chimeric human-mouse monoclonal IgG1 antibody that has been the first anti-EGFR targeted therapy to enter clin. evaluation in cancer patients in Phase II and III studies, alone or in combination with conventional therapies, such as radiotherapy and chemotherapy. A number of small mol. inhibitors of the EGFR tyrosine kinase enzymic activity is also in development. OSI-774 and ZD1839 (Iressa) are currently in Phase II and III development, resp. ZD1839, a p.o. active, selective quinazoline derivative has demonstrated promising in vitro and in vivo antitumor activity. Preliminary results from Phase I and II trials in patients with advanced disease demonstrate that ZD1839 and OSI-774 have an acceptable tolerability profile and promising clin. efficacy in patients with a variety of tumor types. This mini-review describes the EGFR inhibitors in clin. development.

IT 289499-45-2, PD183805
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting the epidermal growth factor receptor as a novel approach in the treatment of cancer)

RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

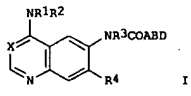
L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:762992 HCAPLUS
DOCUMENT NUMBER: 135:303907
TITLE: Preparation of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction.
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K.-G., Germany
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077104	A1	20011018	WO 2001-EP3694	20010331
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10017539	A1	20011011	DE 2000-10017539	20000408
DE 10040525	A1	20020228	DE 2000-10040525	20000818
CA 2403152	AA	20011018	CA 2001-2403152	20010331
AU 2001063831	A5	20011023	AU 2001-63831	20010331
EP 1280798	A1	20030205	EP 2001-938076	20010331
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003530395	T2	20031014	JP 2001-575577	20010331

PRIORITY APPLN. INFO.:
DE 2000-10017539 A 20000408
DE 2000-10040525 A 20000818
WO 2001-EP3694 W 20010331

OTHER SOURCE(S): MARPAT 135:303907
GI



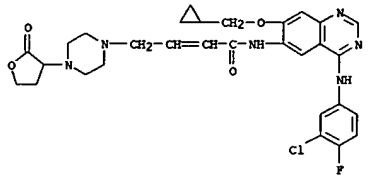
I

AB Title compds. [I; X = NCN, N; R1 = H, alkyl; R2 = (substituted) Ph, PhCH2, PhCH2CH2; R3 = H, alkyl; R4 = H, alkoxy, cycloalkoxy, cycloalkylalkoxy; A = (substituted) vinylene; B = bond, (fluoro)alkylene; D = substituted pyrrolidinyl, piperidinyl, piperazinyl, etc.], were prepared Thus, 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(piperazin-1-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline (preparation given) in THF was treated with Et3N and then with 3-bromodihydrofuran-2-one in THF under ice cooling followed by stirring for 48 h at room temperature to give 56% 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-[4-(2-oxotetrahydrofuran-3-yl)piperazin-1-yl]-1-oxo-2-buten-1-yl]amino]-7-

L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)
cyclopropylmethoxyquinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 0.05 nM.

IT 365532-35-0P 365532-36-1P 365532-37-2P
365532-39-4P 365532-40-7P 365532-41-8P
365532-42-9P 365532-44-1P 365532-45-2P
365532-46-3P 365532-47-4P 365532-48-5P
365532-49-6P 367282-07-3P 367282-12-0P
367282-15-3P 367282-23-3P 367282-25-5P
367282-27-7P 367282-29-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction)

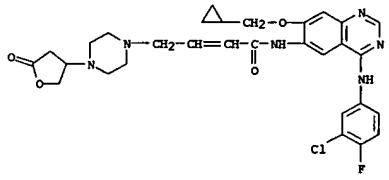
RN 365532-35-0 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(tetrahydro-2-oxo-3-furanyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)



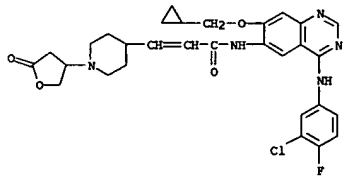
RN 365532-36-1 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[[(2R)-tetrahydro-5-oxo-2-furanyl]methyl]-1-piperazinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



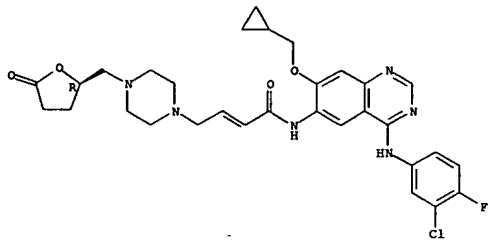
RN 365532-40-7 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-3-[1-(tetrahydro-5-oxo-3-furanyl)-4-piperidinyl]- (9CI) (CA INDEX NAME)



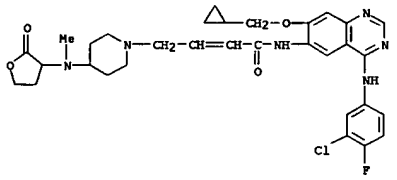
RN 365532-41-8 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[[(2S)-tetrahydro-5-oxo-2-furanyl]carbonyl]-1-piperazinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

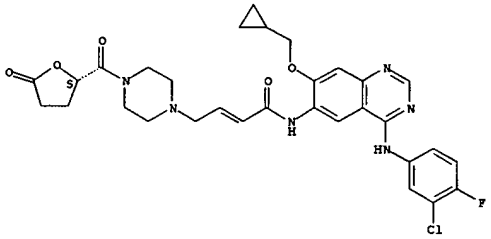


RN 365532-37-2 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[methyl(tetrahydro-2-oxo-3-furanyl)amino]-1-piperidinyl]- (9CI) (CA INDEX NAME)

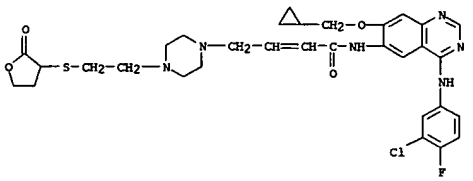


RN 365532-39-4 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(tetrahydro-5-oxo-3-furanyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)

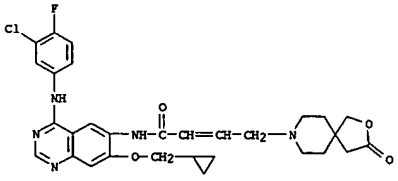
L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 365532-42-9 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[2-[(tetrahydro-2-oxo-3-furanyl)thio]ethyl]-1-piperazinyl]- (9CI) (CA INDEX NAME)

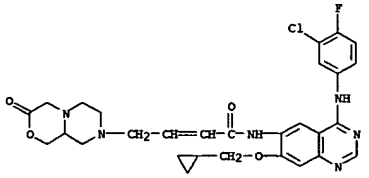


RN 365532-44-1 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(3-oxo-2-oxa-8-azaspiro[4.5]dec-8-yl)- (9CI) (CA INDEX NAME)

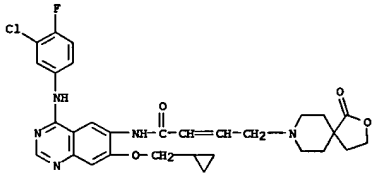


L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

RN 365532-45-2 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(hexahydro-3-oxopyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-(9CI) (CA INDEX NAME)

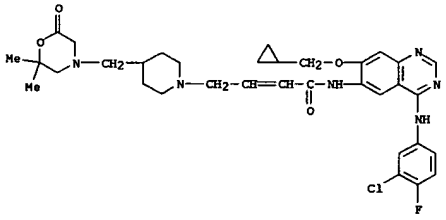


RN 365532-46-3 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1-oxo-2-oxa-8-azaspiro[4.5]dec-8-yl)- (9CI) (CA INDEX NAME)

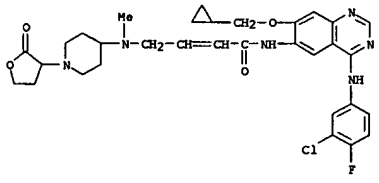


RN 365532-47-4 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(hexahydro-1-oxopyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-(9CI) (CA INDEX NAME)

L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



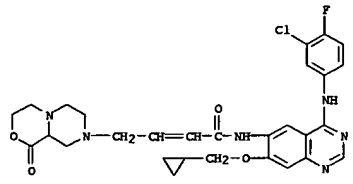
RN 367282-07-3 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl[1-(tetrahydro-2-oxo-3-furanyl)-4-piperidinyl]amino]- (9CI) (CA INDEX NAME)



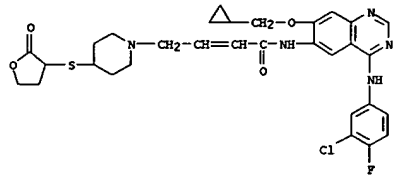
RN 367282-12-0 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl[1-[[(2S)-tetrahydro-5-oxo-2-furanyl]carbonyl]-4-piperidinyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



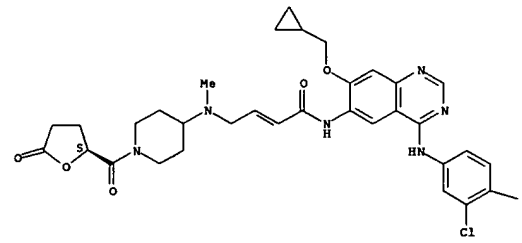
RN 365532-48-5 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[(tetrahydro-2-oxo-3-furanyl)thio]-1-piperidinyl]-(9CI) (CA INDEX NAME)



RN 365532-49-6 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[(2,2-dimethyl-6-oxo-4-morpholinyl)methyl]-1-piperidinyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

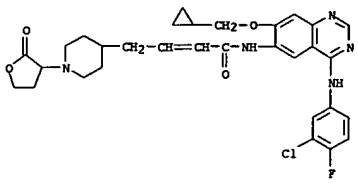
PAGE 1-A



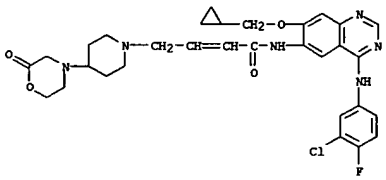
PAGE 1-B

RN 367282-15-3 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[1-(tetrahydro-2-oxo-3-furanyl)-4-piperidinyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



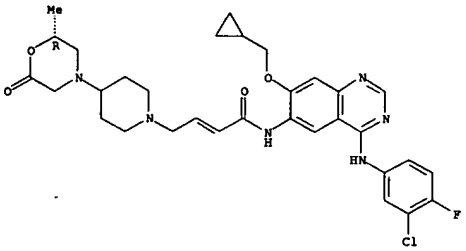
RN 367282-23-3 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(2-oxo-4-morpholinyl)-1-piperidinyl]- (9CI) (CA INDEX NAME)



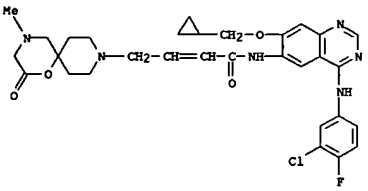
RN 367282-25-5 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[(2R)-2-methyl-6-oxo-4-morpholinyl]-1-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

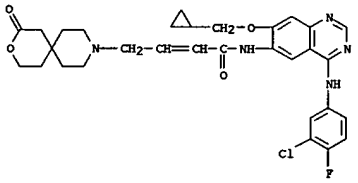


RN 367282-27-7 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(4-methyl-2-oxo-1-oxa-4,9-diazaspiro[5.5]undec-9-yl)- (9CI) (CA INDEX NAME)

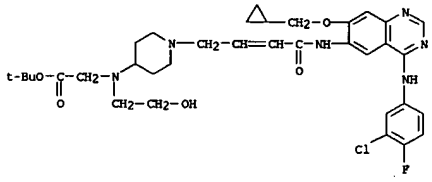


RN 367282-29-9 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(2-oxo-3-oxa-9-azaspiro[5.5]undec-9-yl)- (9CI) (CA INDEX NAME)

L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



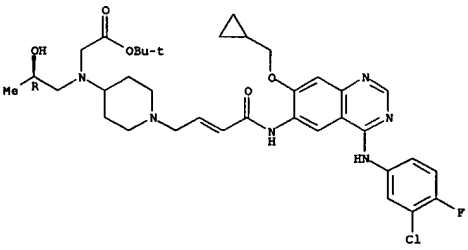
IT 367283-05-4 367283-07-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction)
RN 367283-05-4 HCAPLUS
CN Glycine, N-[1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-4-piperidinyl]-N-(2-hydroxyethyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



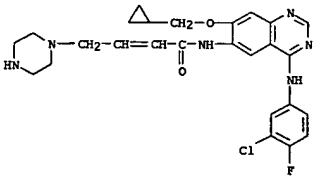
RN 367283-07-6 HCAPLUS
CN Glycine, N-[1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-4-piperidinyl]-N-[(2R)-2-hydroxypropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

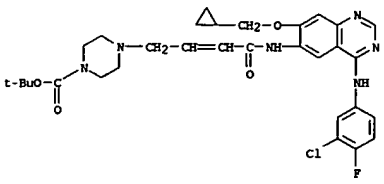


IT 290303-47-8P 290304-01-7P 365532-06-5P
365532-07-6P 365532-18-9P 365532-19-0P
367282-36-8P 367282-44-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction)
RN 290303-47-8 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1-piperazinyl)- (9CI) (CA INDEX NAME)

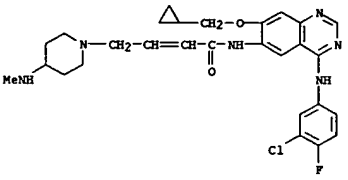


RN 290304-01-7 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

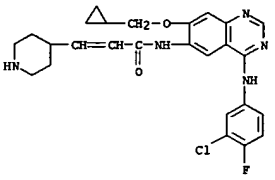
L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



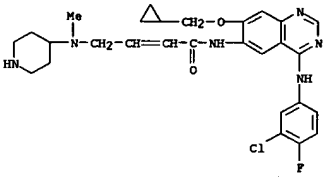
RN 365532-06-5 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(methylamino)-1-piperidinyl]- (9CI) (CA INDEX NAME)



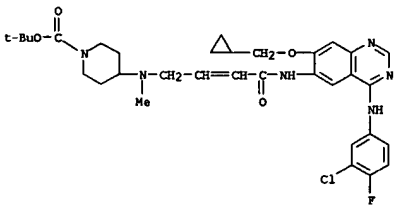
RN 365532-07-6 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-3-(4-piperidinyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



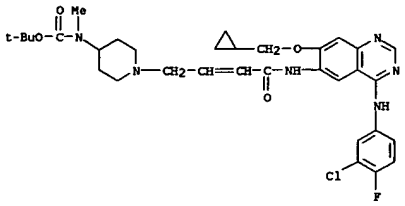
RN 367282-44-8 HCAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]methylamino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



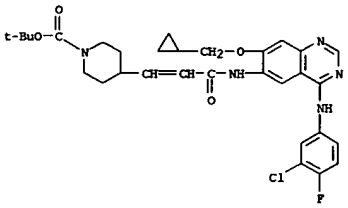
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

RN 365532-18-9 HCAPLUS
CN Carbamic acid, [1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-4-piperidinyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 365532-19-0 HCAPLUS
CN 1-Piperidinecarboxylic acid, 4-[3-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-3-oxo-1-propenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 367282-36-8 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(methyl-4-piperidinylamino)- (9CI) (CA INDEX NAME)

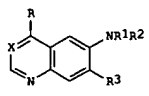
L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:747043 HCAPLUS
DOCUMENT NUMBER: 135:303901
TITLE: Bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction
INVENTOR(S): Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma KG, Germany
SOURCE: Ger. Offen., 28 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10017539	A1	20011011	DE 2000-10017539	20000408
US 2001044435	A1	20011122	US 2001-816003	20010323
US 6627634	B2	20030930		
CA 2403152	AA	20011018	CA 2001-2403152	20010331
WO 2001077104	A1	20011018	WO 2001-EP3694	20010331
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001063831	A5	20011023	AU 2001-63831	20010331
EP 1280798	A1	20030205	EP 2001-938076	20010331
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003530395	T2	20031014	JP 2001-575577	20010331

PRIORITY APPLN. INFO.:
DE 2000-10017539 A 20000408
DE 2000-10040525 A 20000818
WO 2001-EP3694 W 20010331

OTHER SOURCE(S): MARPAT 135:303901
GI



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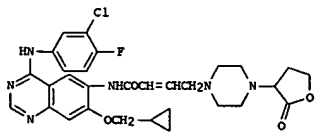


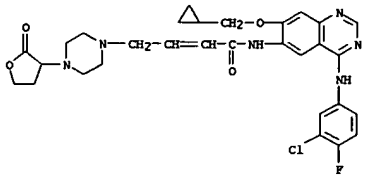
II

L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

AB Bicyclic heterocycles I [X = N, CCN; R = substituted NH2; R1 = H, alkyl; R2 = acyl; R3 = H, (un)substituted alkoxy, cycloalkoxy, tetrahydrofuranyloxy, tetrahydropyranyloxy, tetrahydrofuranylmethoxy, tetrahydropyranylmethoxy] were prepared for use as inhibitors of tyrosine kinase-mediated signal transduction for treatment of tumors and diseases of the lung and airway. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-7-fluoro-6-nitroquinazoline was treated with cyclopropylmethanol, followed by reduction to the amine, reaction with 4-bromocrotonic acid and N-tert.-butoxycarbonylpiperazine, and deblocking to give the quinazoline II. II had an IC50 for inhibition of epidermal growth factor dependent proliferation of 0.05 nM.

IT 365532-35-0P 365532-39-4P 365532-42-9P
365532-45-2P 365532-47-4P 365532-48-5P
365532-49-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction)

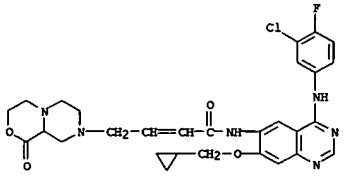
RN 365532-35-0 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(tetrahydro-2-oxo-3-furanyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)



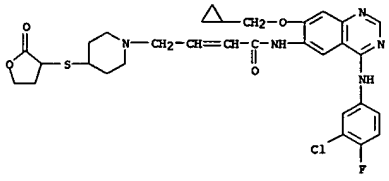
RN 365532-39-4 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(tetrahydro-5-oxo-3-furanyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

RN 365532-47-4 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(hexahydro-1-oxopyrazino[2,1-c][1,4]oxazin-8(1H)-yl)- (9CI) (CA INDEX NAME)

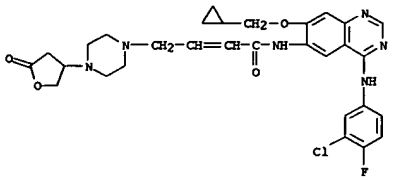


RN 365532-48-5 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[(tetrahydro-2-oxo-3-furanyl)thio]-1-piperidinyl]- (9CI) (CA INDEX NAME)

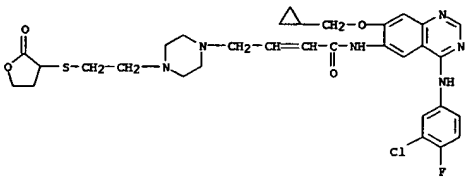


RN 365532-49-6 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[(2,2-dimethyl-6-oxo-4-morpholinyl)methyl]-1-piperidinyl]- (9CI) (CA INDEX NAME)

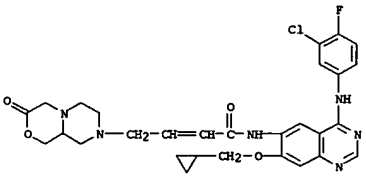
L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



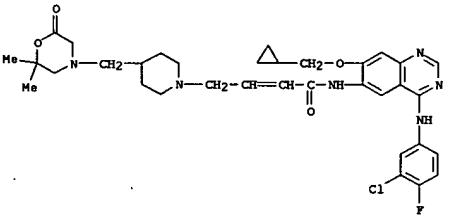
RN 365532-42-9 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[2-[(tetrahydro-2-oxo-3-furanyl)thio]ethyl]-1-piperazinyl]- (9CI) (CA INDEX NAME)



RN 365532-45-2 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(hexahydro-3-oxopyrazino[2,1-c][1,4]oxazin-8(1H)-yl)- (9CI) (CA INDEX NAME)

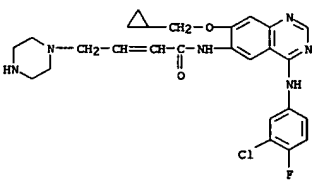


L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



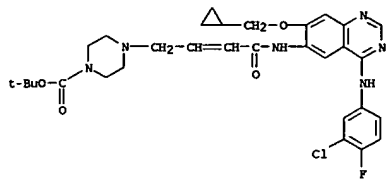
IT 290303-47-8P 290304-01-7P 365532-06-5P
365532-07-6P 365532-10-1P 365532-18-9P
365532-19-0P 365532-21-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction)

RN 290303-47-8 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1-piperazinyl)- (9CI) (CA INDEX NAME)

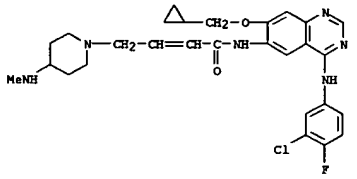


RN 290304-01-7 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

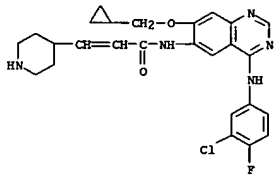
L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



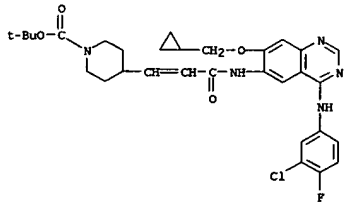
RN 365532-06-5 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(methylamino)-1-piperidinyl]- (9CI) (CA INDEX NAME)



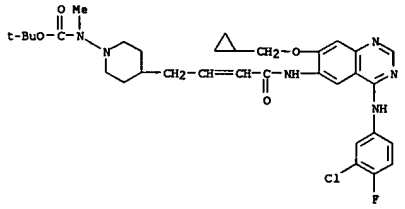
RN 365532-07-6 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-3-(4-piperidinyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 365532-21-4 HCAPLUS
CN Carbamic acid, [4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-1-piperidinyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



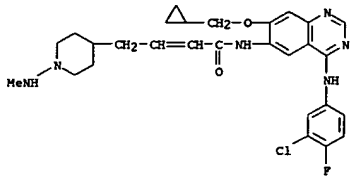
IT 365532-36-1P 365532-37-2P 365532-38-3P
365532-40-7P 365532-41-8P 365532-43-0P
365532-44-1P 365532-46-3P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction)

RN 365532-36-1 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[[(2R)-tetrahydro-5-oxo-2-furanyl]methyl]-1-piperazinyl]- (9CI) (CA INDEX NAME)

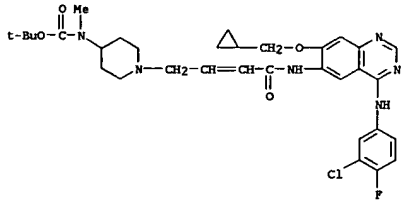
Absolute stereochemistry.
Double bond geometry unknown.

L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

RN 365532-10-1 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[1-(methylamino)-4-piperidinyl]- (9CI) (CA INDEX NAME)

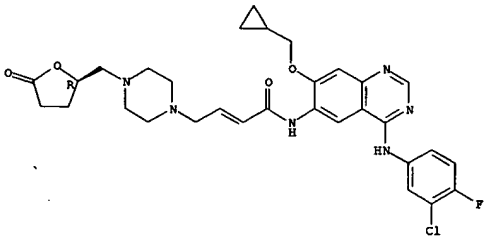


RN 365532-18-9 HCAPLUS
CN Carbamic acid, [1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-4-piperidinyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

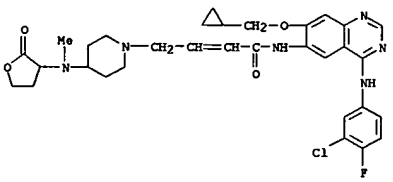


RN 365532-19-0 HCAPLUS
CN 1-Piperidinecarboxylic acid, 4-[3-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-3-oxo-1-propenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

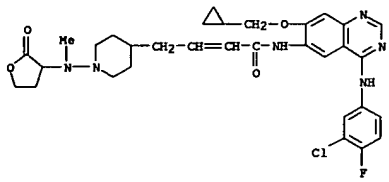


RN 365532-37-2 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[methyl(tetrahydro-2-oxo-3-furanyl)amino]-1-piperidinyl]- (9CI) (CA INDEX NAME)

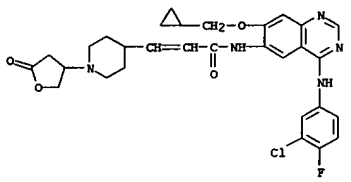


RN 365532-38-3 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[1-[methyl(tetrahydro-2-oxo-3-furanyl)amino]-4-piperidinyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



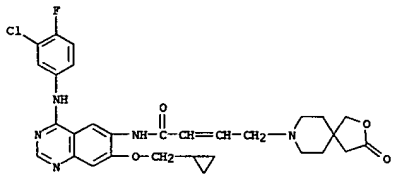
RN 365532-40-7 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-3-[1-(tetrahydro-5-oxo-3-furanyl)-4-piperidinyl]- (9CI) (CA INDEX NAME)



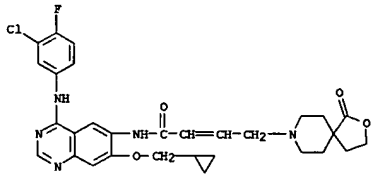
RN 365532-41-8 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[[(2S)-tetrahydro-5-oxo-2-furanyl]carbonyl]-1-piperazinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

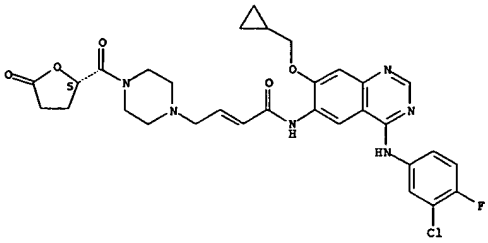
L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



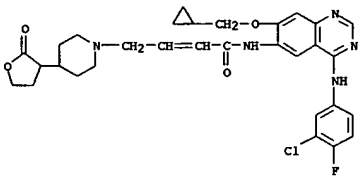
RN 365532-46-3 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1-oxo-2-oxa-8-azaspiro[4.5]dec-8-yl)- (9CI) (CA INDEX NAME)



L4 ANSWER 18 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 365532-43-0 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(tetrahydro-2-oxo-3-furanyl)-1-piperidinyl]- (9CI) (CA INDEX NAME)



RN 365532-44-1 HCAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(3-oxo-2-oxa-8-azaspiro[4.5]dec-8-yl)- (9CI) (CA INDEX NAME)

L4 ANSWER 19 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:380438 HCAPLUS
DOCUMENT NUMBER: 135:24657
TITLE: Selective cellular targeting: multifunctional delivery vehicles
INVENTOR(S): Glazier, Arnold
PATENT ASSIGNEE(S): Drug Innovation & Design, Inc., USA
SOURCE: PCT Int. Appl., 981 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

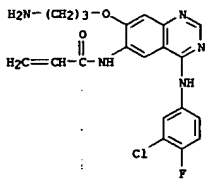
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001036003	A2	20010525	WO 2000-US31262	20001114
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2391534	AA	20010525	CA 2000-2391534	20001114
AU 2001016075	A5	20010530	AU 2001-16075	20001114
EP 1255567	A1	20021113	EP 2000-978631	20001114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003138432	A1	20030724	US 2000-738625	20001215
PRIORITY APPLN. INFO.:			US 1999-165485P	P 19991115
			US 2000-239478P	P 20001011
			US 2000-241937P	P 20001020
			WO 2000-US31262	W 20001114
			US 2000-712465	B1 20001115

AB The present invention relates to the compns., methods, and applications of a novel approach to selective cellular targeting. The purpose of this invention is to enable the selective delivery and/or selective activation of effector mols. to target cells for diagnostic or therapeutic purposes. The present invention relates to multi-functional prodrugs or targeting vehicles wherein each functionality is capable of enhancing targeting selectivity, affinity, intracellular transport, activation or detoxification. The present invention also relates to ultralow dose, multiple target, multiple drug chemotherapy and targeted immunotherapy for cancer treatment.

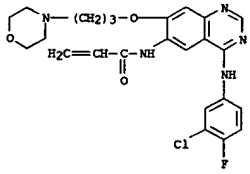
IT 341551-81-3P
RL: PNU (Preparation, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(multifunctional delivery vehicles for selective cellular targeting of drugs)

RN 341551-81-3 HCAPLUS
CN 2-Propenamide, N-[7-(3-aminopropoxy)-4-[(3-chloro-4-fluorophenyl)amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 19 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



L4 ANSWER 20 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:367797 HCAPLUS
DOCUMENT NUMBER: 135:102151
TITLE: Akt, MAPK (Erk1/2), and p38 act in concert to promote apoptosis in response to ErbB receptor family inhibition
AUTHOR(S): Nelson, James M.; Fry, David W.
CORPORATE SOURCE: Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
SOURCE: Journal of Biological Chemistry (2001), 276(18), 14842-14847
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The ErbB receptor family is implicated in the malignant transformation of several tumor types and is over-expressed frequently in breast, ovarian, and other tumors. The mechanism by which CI-1033 and gemcitabine, either singly or in combination, kill tumor cells was examined in two breast lines, MDA-MB-453 and BT474; both overexpress the ErbB-2 receptor. CI-1033, a potent inhibitor of the ErbB family of receptor tyrosine kinases, reduced levels of activated Akt in MDA-MB-453 cells. This effect alone, however, did not induce apoptosis in these cells. Gemcitabine treatment resulted in a moderate increase in the percentage of apoptotic cells that was accompanied by activation of p38 and MAPK (ERK1/2). CI-1033 given 24 h after gemcitabine produced a significant increase in the apoptotic fraction over treatment with either drug alone. During the combined treatment p38 remained activated, whereas Akt and activated MAPK were suppressed. Substitution of CI-1033 with the phosphatidylinositol 3-kinase inhibitor LY294002 and the MAPK/ERK kinase inhibitor PD098059 in combination with gemcitabine produced the same results as the combination of CI-1033 and gemcitabine. P38 suppression by SB203580 prevented the enhanced cell kill by CI-1033. In contrast to MDA-MB-453, BT474 cells exhibited activated p38 under unstressed conditions as well as activated Akt and MAPK. Treatment of BT474 cells with CI-1033 inhibited both the phosphorylation of Akt and MAPK and resulted in a 47% apoptotic fraction. Gemcitabine did not cause apoptosis in the BT474 cells. These data indicate that suppression of Akt and MAPK in the presence of activated p38 results in cell death and a possible mechanism for the enhanced apoptosis produced by the combination of CI-1033 and gemcitabine in MDA-MB-453 cells. Furthermore, tumors that depend on ErbB receptor signaling for survival and exhibit activated p38 in the basal state may be susceptible to apoptosis by CI-1033 as a single agent.

IT 267243-28-7, CI-1033
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(Akt, MAPK (Erk1/2), and p38 act in concert to promote apoptosis in human breast carcinoma in response to ErbB receptor family inhibition)

RN 267243-28-7 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 21 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

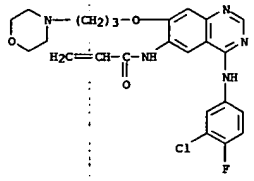
ACCESSION NUMBER: 2001:125550 HCAPLUS
DOCUMENT NUMBER: 134:348032
TITLE: The HER tyrosine kinase inhibitor CI1033 enhances cytotoxicity of 7-ethyl-10-hydroxycamptothecin and topotecan by inhibiting breast cancer resistance protein-mediated drug efflux
AUTHOR(S): Erlichman, Charles; Boerner, Scott A.; Hallgren, Christopher G.; Spieker, Rebecca; Wang, Xiao-Yang; James, C. David; Scheffer, George L.; Maliepaard, Marc; Ross, Douglas D.; Bible, Keith C.; Kaufmann, Scott H.
CORPORATE SOURCE: Division of Medical Oncology, Mayo Clinic, Mayo Graduate School, Rochester, MN, 55905, USA
SOURCE: Cancer Research (2001), 61(2), 739-748
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Because the activities of HER family members are elevated and/or aberrant in a variety of human neoplasms, these cell surface receptors are receiving increasing attention as potential therapeutic targets. In the present study, we examined the effect of combining the HER family tyrosine kinase inhibitor CI1033 (PD 183805) with the topoisomerase (topo) I poison 7-ethyl-10-hydroxycamptothecin (SN-38), the active metabolite of irinotecan, in a number of different cell lines. Colony-forming assays revealed that the antiproliferative effects of simultaneous treatment with CI1033 and SN-38 were synergistic in T98G glioblastoma cells and HCT8 colorectal carcinoma cells, whereas sequential treatments were additive at best. In addnl. studies examining the mechanistic basis for these findings in T98G cells, immunoblotting revealed that the inhibitory effects of CI1033 on epidermal growth factor receptor autophosphorylation were unaffected by SN-38. Likewise, CI1033 had no effect on topo I polypeptide levels, localization, or activity. Nonetheless, CI1033 markedly enhanced the number of covalent topo I-DNA complexes stabilized by SN-38 or the related agent topotecan (TPT). Anal. of intracellular SN-38 levels by high-performance liquid chromatog. and intracellular TPT levels by flow microfluorometry revealed that CI1033 increased the steady-state accumulation of SN-38 and TPT by 9.4 ± 1.9- and 1.8 ± 0.2-fold, resp. Further evaluation revealed that the initial rate of TPT uptake was unaffected by CI1033, whereas the rate of efflux was markedly diminished. Addnl. studies demonstrated that T98G and HCT8 cells express the breast cancer resistance protein (BCRP), a recently cloned ATP binding cassette transporter. Moreover, CI1033 enhanced the uptake and cytotoxicity of SN-38 and TPT in cells transfected with BCRP but not empty vector. Conversely, CI1033 accumulation was diminished in cells expressing BCRP, suggesting that CI1033 is a substrate for this efflux pump. These results indicate that CI1033 can modulate the accumulation and subsequent cytotoxicity of two widely used topo I poisons in cells that have no history of previous exposure to these agents.

IT 289499-45-2, CI 1033
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(HER tyrosine kinase inhibitor CI1033 interactions with SN-38 and topotecan in cancer treatment)

RN 289499-45-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L4 ANSWER 21 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



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REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

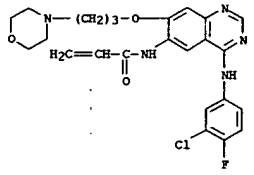
ACCESSION NUMBER: 2000:828300 HCAPLUS
DOCUMENT NUMBER: 135:57892
TITLE: Radiosensitization of human breast cancer cells by a novel ErbB family receptor tyrosine kinase inhibitor
AUTHOR(S): Rao, G. S.; Murray, S.; Ethier, S. P.
CORPORATE SOURCE: Department of Radiation Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA
SOURCE: International Journal of Radiation Oncology, Biology, Physics (2000), 48(5), 1519-1528
CODEN: IOBPD3; ISSN: 0360-3016
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purpose: Overexpression of the ErbB family of growth factor receptors is present in a wide variety of human tumors and is correlated with poor prognosis. The purpose of this study was to determine the effects of a novel small mol. ErbB tyrosine kinase inhibitor, CI-1033, in combination with ionizing radiation on breast cancer cell growth and survival. Materials & Methods: Growth assays were performed on ErbB-overexpressing human breast cancer cells developed in our laboratory in the presence of 0.1-1.0 μM CI-1033 (Parke Davis). Clonogenic survival assays were performed in the presence of ionizing radiation with or without CI-1033. For some expts., clonogen nos., defined as the product of surviving fraction and total number of cells, were calculated at each time point during a course of multifraction radiation. Results: CI-1033 potently inhibited the growth of ErbB-overexpressing breast cancer cells. A single 48-h exposure of 1 μM CI-1033 resulted in growth inhibition for 7 days, whereas three times weekly administration resulted in sustained growth inhibition. Clonogenic survival was modestly decreased after a 7-day exposure to CI-1033. Exposure to both CI-1033 and radiation (6 Gy) yielded a 23-fold decrease in clonogenic survival compared to radiation alone. In a multifraction experiment, exposure to CI-1033 and three 5-Gy fractions of gamma radiation decreased the total number of clonogens in the population by 65-fold compared to radiation alone. Conclusion: CI-1033 results in potent growth inhibition and modest cytotoxicity of ErbB-overexpressing breast cancer cells, and has synergistic effects when combined with ionizing radiation. These data suggest that CI-1033 may have excellent clin. potential both alone and in combination with radiation therapy.

IT 267243-28-7, CI-1033
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(radiosensitization of human breast cancer cells by ErbB family receptor tyrosine kinase inhibitor)

RN 267243-28-7 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 22 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

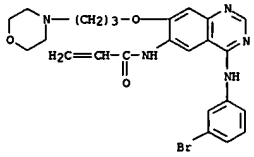
L4 ANSWER 23 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:481416 HCAPLUS
DOCUMENT NUMBER: 134:216784
TITLE: Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(phenylamino)quinazoline- and 4-(phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions. [Erratum to document cited in CA132:317628]
AUTHOR(S): Smaill, Jeff B.; Rewcastle, Gordon W.; Bridges, Alexander J.; Zhou, Hairong; Showalter, H. D. Hollis; Fry, David W.; Nelson, James M.; Sherwood, Veronika; Elliott, William L.; Vincent, Patrick W.; DeJohn, Dana E.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty Medical and Health Sciences, The Univ. Auckland, Auckland, N. Z.
SOURCE: Journal of Medicinal Chemistry (2000), 43(16), 3199
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Six author names were inadvertently omitted from the author contribution line. The complete author list is as follows: Jeff B. Smaill, Gordon W. Rewcastle, Alexander J. Bridges, Hairong Zhou, H. D. Hollis Showalter, David W. Fry, James M. Nelson, Veronika Sherwood, William L. Elliott, Patrick W. Vincent, Dana E. DeJohn, Joseph A. Loo, Kenneth D. Greis, O. Helen Chan, Eric L. Reyner, Elke Lipka, and William A. Denny.

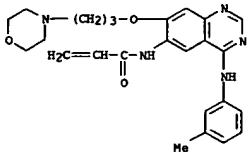
IT 198959-99-8P 198960-00-8P 198960-01-9P
198960-02-0P 198960-04-2P 198960-05-3P
267243-26-5P 267243-27-6P 267243-28-7P
267243-29-8P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(antitumor and EGFR enzyme-inhibiting SAR of quinazolines (Erratum))

RN 198959-99-8 HCAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 198960-00-8 HCAPLUS
CN 2-Propenamide, N-[4-[(3-methylphenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 23 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 198960-01-9 HCAPLUS
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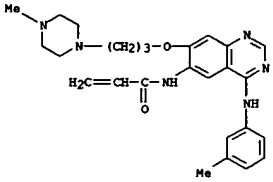
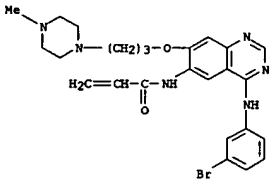
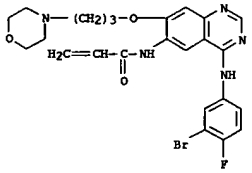


RN 198960-02-0 HCAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-methyl-1-piperazinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 198960-04-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(1H-imidazol-1-yl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 23 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 267243-28-7 HCAPLUS
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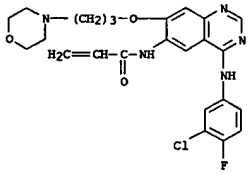

RN 267243-29-8 HCAPLUS
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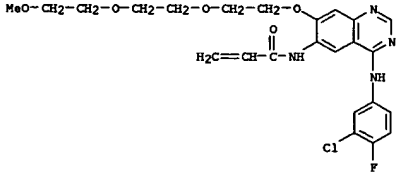
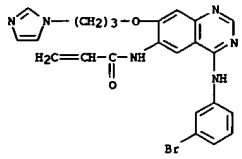


L4 ANSWER 23 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 198960-05-3 HCAPLUS
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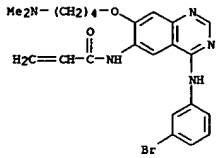

RN 267243-26-5 HCAPLUS
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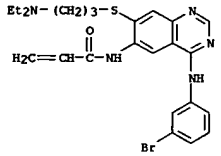


RN 267243-27-6 HCAPLUS
CN 2-Propenamide, N-[4-[(3-bromo-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

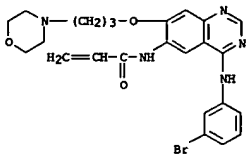
L4 ANSWER 24 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:164843 HCAPLUS
DOCUMENT NUMBER: 132:317628
TITLE: Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(Phenylamino)quinazoline- and 4-(Phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions
AUTHOR(S): Smaill, Jeff B.; Rewcastle, Gordon W.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Showalter, H. D. Hollis; Vincent, Patrick W.; Elliott, William L.; Denny, William A.
CORPORATE SOURCE: Auckland Cancer Society Research Centre Faculty of Medical and Health Sciences, The University of Auckland, Auckland, N. Z.
SOURCE: Journal of Medicinal Chemistry (2000), 43(7), 1380-1397
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

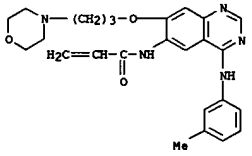
AB 4-Anilinoquinazoline- and 4-anilinopyrido[3,2-d]pyrimidine-6-acrylamides substituted with solubilizing 7-alkylamine or 7-alkoxyamine side chains were prepared by reaction of the corresponding 6-amines with acrylic acid or acrylic acid anhydrides. In the pyrido[3,2-d]pyrimidine series, the intermediate 6-amino-7-alkylamines were prepared from 7-bromo-6-fluoropyrido[3,2-d]pyrimidine via Stille coupling with the appropriate stannane under palladium(0) catalysis. This proved a versatile method for the introduction of cationic solubilizing side chains. The compds. were evaluated for their inhibition of phosphorylation of the isolated EGFR enzyme and for inhibition of EGF-stimulated autophosphorylation of EGFR in A431 cells and of heregulin-stimulated autophosphorylation of erbB2 in MDA-MB 453 cells. Quinazoline analogs with 7-alkoxyamine solubilizing groups were potent irreversible inhibitors of the isolated EGFR enzyme, with IC50[app] values from 2 to 4 nM, and potently inhibited both EGFR and erbB2 autophosphorylation in cells. 7-Alkylamino- and 7-alkoxyaminopyrido[3,2-d]pyrimidines were also irreversible inhibitors with equal or superior potency against the isolated enzyme but were less effective in the cellular autophosphorylation assays. Both quinazoline- and pyrido[3,2-d]pyrimidine-6-acrylamides bound at the ATP site alkylating cysteine 773, as shown by electrospray ionization mass spectrometry, and had similar rates of absorptive and secretory transport in Caco-2 cells. A comparison of two 7-propoxymorpholide analogs showed that the pyrido[3,2-d]pyrimidine-6-acrylamide had greater amide instability and higher acrylamide reactivity, being converted to glutathione adducts in cells more rapidly than the corresponding quinazoline. This difference may contribute to the observed lower cellular potency of the pyrido[3,2-d]pyrimidine-6-acrylamides. Selected compds. showed high in vivo activity against A431 xenografts on oral dosing, with the quinazolines being superior to the pyrido[3,2-d]pyrimidines. Overall, the quinazolines proved superior to previous analogs in terms of aqueous solubility, potency, and in vivo antitumor activity, and one example (CI 1033) has been selected for clin. evaluation.

IT 198959-99-8P 198960-00-8P 198960-01-9P
198960-02-0P 198960-04-2P 198960-05-3P
267243-26-5P 267243-27-6P 267243-28-7P
267243-29-8P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP

L4 ANSWER 24 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)
(Preparation)
(antitumor and EGFR enzyme-inhibiting SAR of quinazolines)
RN 198959-99-8 HCAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

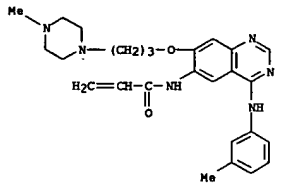


RN 198960-00-8 HCAPLUS
CN 2-Propenamide, N-[4-[(3-methylphenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

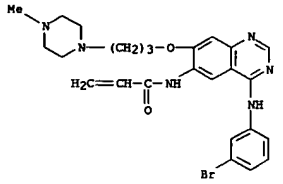


RN 198960-01-9 HCAPLUS
CN 2-Propenamide, N-[4-[(3-methylphenyl)amino]-7-[3-(4-methyl-1-piperazinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

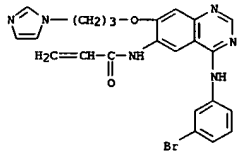
L4 ANSWER 24 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 198960-02-0 HCAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-methyl-1-piperazinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

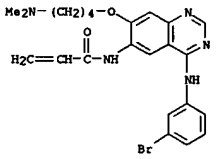


RN 198960-04-2 HCAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(1H-imidazol-1-yl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

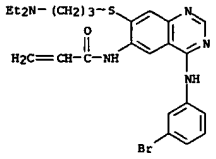


RN 198960-05-3 HCAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[4-(dimethylamino)butoxy]-6-

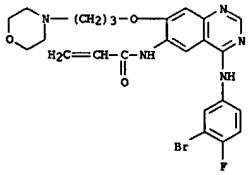
L4 ANSWER 24 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)
quinazolinyl]- (9CI) (CA INDEX NAME)



RN 267243-26-5 HCAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[[3-(diethylamino)propyl]thio]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

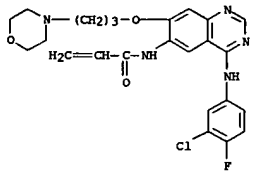


RN 267243-27-6 HCAPLUS
CN 2-Propenamide, N-[4-[(3-bromo-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

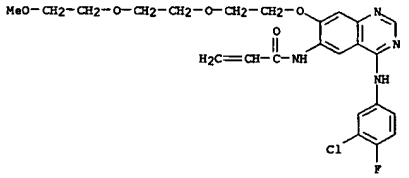


RN 267243-28-7 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 24 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 267243-29-8 HCAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:113656 HCAPLUS
DOCUMENT NUMBER: 130:168387
TITLE: Irreversible inhibitors of tyrosine kinases
INVENTOR(S): Bridges, Alexander James
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906378	A1	19990211	WO 1998-US15784	19980729
W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9887607	A1	19990222	AU 1998-87607	19980729
US 6127374	A	20001003	US 1999-269545	19990325
US 6562818	B1	20030513	US 2000-593031	20000613
PRIORITY APPLN. INFO.:			US 1997-54060P	P 19970729
			WO 1998-US15784	W 19980729
			US 1999-269545	A3 19990325

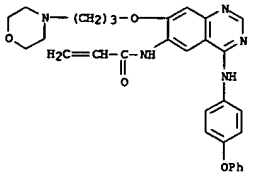
OTHER SOURCE(S): MARPAT 130:168387

AB Pyrimidine derivs. that are irreversible inhibitors of tyrosine kinases are reported. Thus, PhCH2OH was treated with 4-FC6H4NO2 to give 4-PhCH2OC6H4NO2, which was reduced to the amine and used to aminate 4-chloro-6-nitroquinazoline hydrochloride. The resulting 6-nitro-4-[4-benzyloxyanilino]quinazoline hydrochloride was reduced to the amine and acylated to give N-[4-(4-benzyloxyanilino)quinazolin-6-yl]acrylamide (I). I had an IC50 for inhibition of epidermal growth factor receptor tyrosine kinase of 3.6 nM.

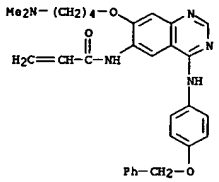
IT 220488-46-0P 220488-47-1P 220488-48-2P
220488-49-3P 220489-87-2P 220489-88-3P
220489-89-4P 220489-90-7P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of anilinoquinazolinylacrylamides and related compds. as tyrosine kinase inhibitors)

RN 220488-46-0 HCAPLUS
CN 2-Propenamide, N-[7-[3-(4-morpholinyl)propoxy]-4-[(4-phenoxyphenyl)amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

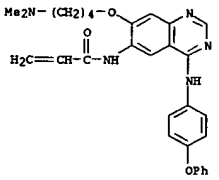
L4 ANSWER 25 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 220488-47-1 HCAPLUS
CN 2-Propenamide, N-[7-[4-(dimethylamino)butoxy]-4-[[4-(phenylmethoxy)phenyl]amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

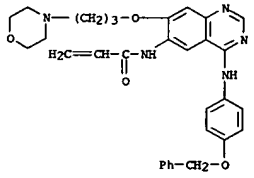


RN 220488-48-2 HCAPLUS
CN 2-Propenamide, N-[7-[4-(dimethylamino)butoxy]-4-[(4-phenoxyphenyl)amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

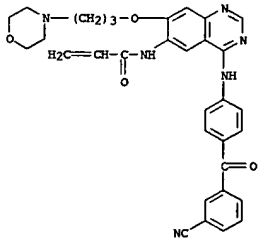


RN 220488-49-3 HCAPLUS
CN 2-Propenamide, N-[7-[3-(4-morpholinyl)propoxy]-4-[[4-

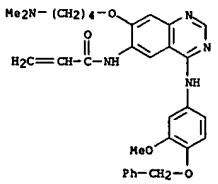
L4 ANSWER 25 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)
(phenylmethoxy)phenyl]amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 220489-87-2 HCAPLUS
CN 2-Propenamide, N-[4-[[4-(3-cyanobenzoyl)phenyl]amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

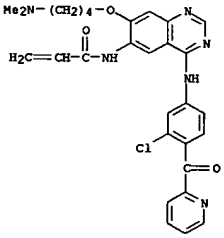


RN 220489-88-3 HCAPLUS
CN 2-Propenamide, N-[7-[4-(dimethylamino)butoxy]-4-[[3-methoxy-4-(phenylmethoxy)phenyl]amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

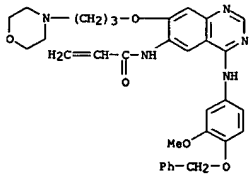


L4 ANSWER 25 OF 25 HCAPLUS COPYRIGHT 2006 ACS on STN (Continued)

RN 220489-89-4 HCAPLUS
CN 2-Propenamide, N-[4-[[3-chloro-4-(2-pyridinylcarbonyl)phenyl]amino]-7-[4-(dimethylamino)butoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 220489-90-7 HCAPLUS
CN 2-Propenamide, N-[4-[[3-methoxy-4-(phenylmethoxy)phenyl]amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT